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Plasmapheresis as a Promising Therapeutic Option to Treat Macrophage Activation Syndrome

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A B S T R A C T

Macrophage activation syndrome (MAS) is a lethal complication of autoimmune conditions. Its diagnosis and management remains challenging till date in view of paucity of standard protocols. Plasmapheresis has shown promise if used early in the course of disease. We hereby describe a case report of a young male patient who presented with multiorgan failure. He was diagnosed with MAS triggered by systemic lupus erythematosus (SLE). He was successfully treated with steroids, cyclophosphamide and plasmapheresis.

1. Introduction

MAS is an uncommon but fatal complication seen in autoimmune diseases. The incidence is estimated to be about 1-10 per million in various studies.[1] Mortality has been reported in 30-70% of patients.[2] It is classically associated with multi-organ involvement. Diagnosis is difficult as it can overlap with underlying disease and commonly confounded by sepsis. Therapeutic protocols are lacking due to rarity of this condition. Early use of plasmapheresis can improve patient outcomes.

2. Case Presentation

A 24 year old gentleman, non-alcoholic and non-smoker was admitted with subacute history of high-grade intermittent fever, nausea, and jaundice since 1 week and oliguria with breathlessness since 2 days. On enquiry, the patient had significant unexplained weight loss over the last 3 months. On examination, the patient had tachycardia, tachypnoea, normotension, icterus, pedal oedema, and abdominal striae. He also had hepatosplenomegaly with ascites, bi-basal rales on lung exam and early encephalopathy. Investigations revealed pancytopenia, negative septic screen, and liver and renal dysfunction with acute hypoxic respiratory failure requiring ventilatory support. Detailed investigations are listed in Table 1. A differential diagnosis of sepsis with thrombotic microangiopathy (TMA); autoimmune disease with probable MAS; secondary infections triggering hemophagocytic lympho-histiocytosis (sHLH) were considered. Autoimmune screening revealed strongly positive anti-nuclear antibodies (ANA), anti-Ro and anti-La antibodies with positive lupus anticoagulant. Patient was initiated on pulse steroids with methylprednisolone 1000 mg for 3 days and cyclophosphamide 500 mg every 2 weeks. Anticoagulation with warfarin was initiated in view of probable anti-phospholipid

antibody syndrome (APLA). Seven haemodialysis sessions and five sessions of plasmapheresis were done for MAS.

Table 1. Investigation

NO	VARIABLES	RESULT
1.	Hemoglobin/White cell Count/Platelet/ C-Reactive Protein/Procalcitonin	10.2/4000/163000/12/0.5
2.	Peripheral smear	Normocytic normochromic anemia/ mild thrombocytopenia/ 3% fragmented RBC seen/ mild neutrophilia
3.	Ferritin/ Triglycerides	**16434** (30-300)/ **971** (<150)
4.	Urea/creatinine	**137/7.2**
5.	Sodium/ Potassium/ Chloride/ Bicarbonate	130/ 4/ 97/ 19
6.	Calcium / Phosphorus/ Alkaline phosphatase	**6.6/ 7.3**/ 297
7.	Protein/ Albumin/ INR	6/ **2.8**
8.	SGOT/ SGPT/ Total Bilirubin/ Direct Bilirubin	**1191/ 224/ 8.2/ 6.7**
9.	Lactate dehydrogenase/ Haptoglobin / Fibrinogen	1857 (120-246) / 77 (30-200)/ 1.82
10.	Antinuclear Antibody	**1:4000** (granular pattern with mitoses)
11.	Interleukin-6/ serum Ceruloplasmin	27.1 (0-7 ng/L)/ 27 (16-31)
12.	Anti SS-A/Anti RO-52/Anti SS-B	Strong positive (**+++**)
13.	Anti LKM(liver-kidney-muscle)/ anti SM AB	1.1 (0-20)- negative/ 12 (0-19)- negative
14.	Anti-HIV 1& 2/ HBsAG/Anti-HCV/ Anti HAV/Anti-HEV/ Leptospira/ CMV/EBV/Brucella	Negative
15.	C3/C4 compliment	**53(** 90-207) / **15** (17-52)
16.	Lupus anticoagulant/ Rheumatoid factor/ Anti B2 glycoprotein 1 AB/ Anti Cardiolipin AB/ p-ANCA/c-ANCA	**Present** /Absent / Absent/ Absent/ Absent/ Absent
17.	Interleukin-2 receptor Alpha (soluble CD25)	**6404** U/ml (223-710)
18.	Urine routine microscopy	Dark amber colour, specific gravity 1.009, Protein 1+, Bilirubin 2+, Blood 1+, 5-10 RBC, 0-2 WBC, muddy brown granular casts+
19.	24 hour urine protein	**1197 mg**
20.	Kidney biopsy	Light microscopy s/o tubular necrosis, 7 unremarkable glomeruli, vessels and interstitium normal. Immunofluorescence- full house positivity ; EM- tubular injury.
21.	USG Abdomen	Markedly **enlarged liver** with diffuse bright echotexture; **spleen mildly enlarged**, normal size kidneys mildly increased echogenicity.

Abbreviation: RBC= Red blood cells, INR= International Normalized Ratio, SGOT= Serum Glutamic Oxaloacetic Transaminase, SGPT= Serum Glutamic Pyruvic Transaminase, Anti SM AB= Anti Smith Antibody, HBsAG= Hepatitis B Surface Antigen, HCV= Hepatitis C Virus, HAV= Hepatitis A Virus, CMV= Cytomegalovirus, EBV= Epstein-Barr virus, ANCA= Antineutrophil cytoplasmic antibody, CD25= Cluster of differentiation 25, WBC= White blood cells, USG= Ultrasound Sonography

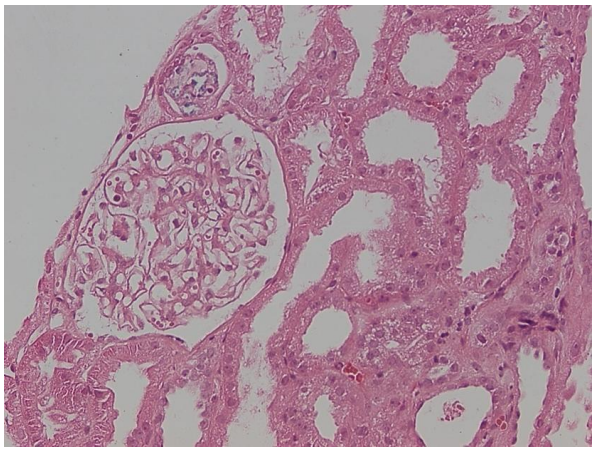

Figure 1. Light microscopy (PAS stain) - Acute tubular injury

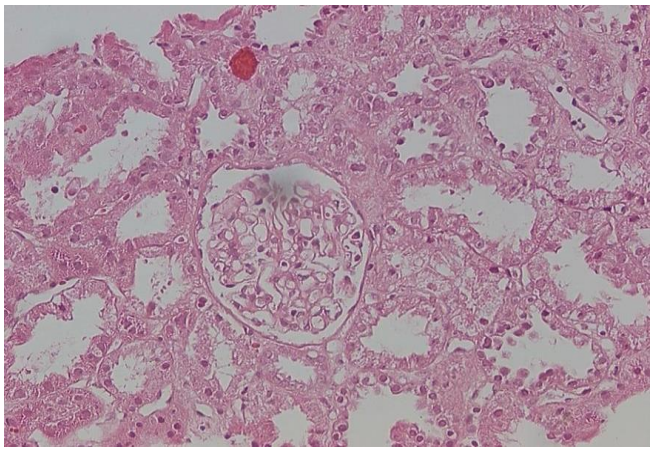

Figure 2. Light microscopy (H&E stain) - Acute tubular injury

Kidney biopsy done upon stabilization excluded TMA and revealed acute tubular necrosis as shown in Figures 1 and 2. The patient responded well and showed complete resolution of acute kidney injury. His creatinine reached a nadir of 0.97 mg/dl and his liver functions also recovered with SGOT 35 IU/L, SGPT 42 IU/L, and total bilirubin 0.5 mg/dL. He was discharged on prednisolone 30 mg, cyclophosphamide therapy 500 mg every 2 weeks for 3 months and warfarin.

3. Discussion

MAS also referred to as secondary haemophagocytic lymphohistiocytosis (sHLH) is a potentially life-threatening complication of autoimmune inflammatory rheumatic diseases (AIIRD), with mortality rates reported to be as high as 30-70%.[2,3] The prevalence rate of MAS in AIIRD is 1.1%, and it is commonly associated with SLE.[4] Abnormal macrophage and T cell hyperactivation along with a systemic cytokine flare are proposed as pathophysiologic mechanisms, which generate a sepsis-like, tissue-damaging, cytopenic phenotype. Patients may present with persistent fever, lymphadenopathy, hepatosplenomegaly and unexplained weight loss. MAS is associated with a haemorrhagic syndrome causing echymotic skin patches, hemoptysis or malena in severe cases. Renal and neurological involvement are very common and associated with worse outcomes. Respiratory involvement includes pulmonary infiltrates and ARDS. Clinical presentation of MAS has considerable overlap with the underlying autoimmune condition or sepsis, making early diagnosis difficult. Thirty percent of cases are diagnosed only at post mortem.[3] Diagnosis of MAS is complicated and often based on multiple criteria that have changed over the years, including the HLH-2004 clinical criteria which required at least the presence of molecular diagnosis consistent with HLH or five out of nine findings that include fever >38.5oC; enlarged spleen; peripheral blood cytopenias; raised triglycerides; hemophagocytosis in either bone marrow, spleen, lymph node or liver; low or absent natural killer (NK) cell activity; high ferritin; high soluble CD25, soluble CD163 or elevated CXCL9.[5] Other features are elevated C-reactive protein (CRP), low erythrocyte sedimentation rate (ESR), elevated transaminases and low fibrinogen.[2] A ferritin level of >10,000 ng/mL is highly sensitive and specific for severe sHLH as was observed in our case. Soluble CD25 reflects T cell and macrophage activation which was also significantly elevated in our patient.[6] The female-to-male ratio in SLE patients is 10:1, but this ratio is reduced for MAS in SLE patients. It was 3.7:1 in seven out of eight studies.[5,7] This suggests that MAS is significantly more common in males suffering from lupus; a finding consistent with our case. Lupus flares are the most common trigger for HLH followed by infections.[7]

SLEDAI scores have been found to be a good risk predictor of MAS in lupus patients, while hydroxychloroquine use and arthritis were associated with a lower risk of MAS.[7] Steroids combined with etoposide, calcineurin inhibitors, Intravenous Immunoglobulin; cyclophosphamide, and anti-IL-1 are often considered as the first-line therapy. Plasmapheresis effectively removes proinflammatory cytokines and reduced the mortality of AIIRD-associated MAS.[3] The benefit of using plasmapheresis early in the course of MAS was also observed by Kinjo N et al.[8] Lorenz et al found plasmapheresis to improve patient outcomes in steroid-refractory MAS.[9] However, therapeutic protocols remain to be defined. High dose Corticosteroids are suggested as the first-line treatment. Pulse methylprednisolone (1 g/d for 3-5 consecutive days) is proposed as initial therapy. Cyclosporine (2-7 mg/kg per day) and anakinra (2-10 mg/kg) are useful in patients with partial response. Tocilizumab has also shown promise in resistant cases. Etoposide has been effective in severe cases with neurological involvement.[10] Risk factors for high mortality include age greater than 50 years, infections, elevated CRP, reduced cell counts on hemogram, liver and renal involvement, presence of MAS.[7] Special considerations should be made especially for elderly and male patients with high ferritin levels and hematological involvement in SLE.

4. Conclusion

MAS is a rare and potentially fatal complication of AIIRD. Diagnosis requires a high degree of suspicion and needs good laboratory support. Early initiation of corticosteroids and plasmapheresis in severe cases can be life saving and help in improving patient outcomes.

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